8. E. S. Nikit-skaya, L. M. Alekseeva, Yu. N. Sheinker, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., No. 12, 1672 (1971).

CONVERSION OF THE QUINOLINE RING TO AN INDOLE RING

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4-Nitro-3-hydroxyquinoline is readily converted to indole derivatives in aqueous alkaline and acetic acid media. The contraction of the quinoline ring to an indole ring under the conditions of mild methylation of 4-nitro-3-hydroxyquinoline in an aqueous alkaline medium proceeds through the formation of the N-methyl derivative of 4-nitro-3-hydroxyquinoline and N-methyl-2-formyl-3-nitroindole. 3-Nitroindole is formed when 4-nitro-3-hydroxyquinoline is heated in aqueous alkali, whereas isatin is formed in acetic acid. The methylation of 4-nitro-3-hydroxyquinoline in refluxing acetic acid leads to N-methylisatin.

We have previously reported that contraction of the pyridine ring to give N-methyl-3-nitroindole (II) in ∿60% yield occurs when 4-nitro-3-hydroxyquinoline (I) is treated with dimethyl sulfate in an aqueous alkaline medium [1].

The formation of indole II from quinoline I under the conditions presented above is a consequence of two chemical transformations: contraction of the pyridine ring and methylation. We were able to ascertain the interrelationship and sequence of the indicated processes. It was found that when dimethyl sulfate is absent, I remains unchanged in an aqueous alkali medium at room temperature, whereas the N-methyl-4-nitro-3-hydroxyquinolinium salt (III) forms indole II smoothly. This indicates the primacy of and the necessity for methylation in ring contraction under mild conditions.

In addition to II, a small amount of a substance that is insoluble in acidic media and was identified as N-methyl-4-nitro-1,2-(or 1,4-)dihydro-2,3-dihydroxyquinoline (IV) is formed both in the case of methylation of quinoline I in alkaline media and in the case of treatment of quaternary compound III with alkali. The carbon atom that is split out during ring contraction was detected in the volatile reaction products in the form of formic acid.

The ring contraction can evidently proceed via two pathways: either with the formation of a C_2—C_4 bond or an N_1—C_3 bond. In the first case the 2-formyl derivative (V) will be formed as an intermediate, while in the second case one might have expected the formation of a nitro derivative of oxindole. The first pathway seemed most likely to us, since it was easy to imagine the possible deformylation of the 2-formyl derivative under the reaction conditions to give II and sodium formate.

In fact, N-methyl-3-nitro-2-formylindole (V) and the known pseudobase IV were isolated when quinoline I was treated with dimethyl sulfate in an aqueous solution of sodium carbonate. Compound III behaves similarly in an aqueous solution of sodium acetate. As expected, V is readily deformylated in an aqueous alkali solution to give II.

Thus, the methylation of quinoline I in an alkaline medium proceeds through the formation of N-methyl derivative III, which undergoes structural conversion to formylindole V with the probable formation of a new C_2—C_4 bond.

Further studies showed that contraction of the quinoline ring may also occur without methylation but under more severe conditions. Thus, 3-nitroindole (IV) is formed in ∿55% yield when I is refluxed for a long time in a 2 N aqueous solution of sodium hydroxide.

We were able to observe ring contraction in media other than alkaline media. When quinoline I is methylated with dimethyl sulfate in acetic acid, N-methylisatin (VII) is formed in ∿7% yield along with a preponderant amount of III. Isatin VIII is formed in 33% yield when I is refluxed in glacial acetic acid. The lack of conformity with the preceding logical

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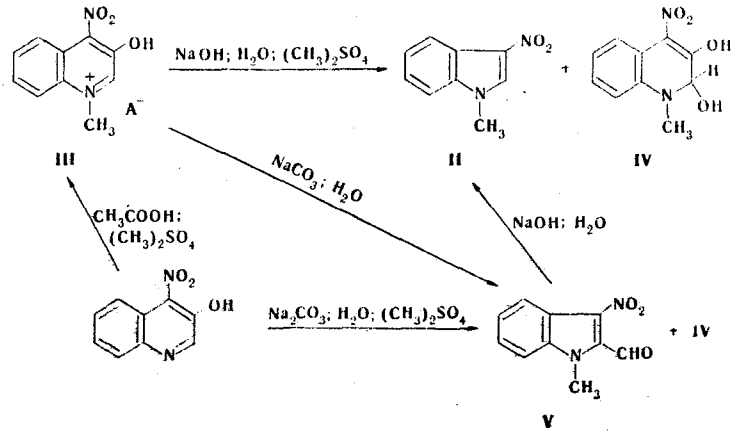
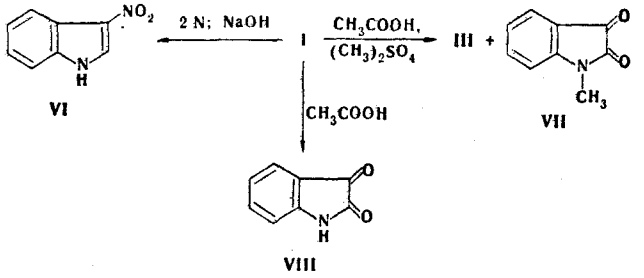
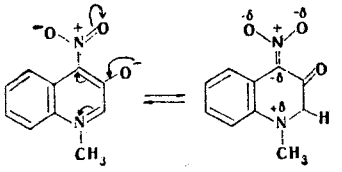


scheme of the yields of VII and VIII, which are formed in the same time in the same solvent, compelled us to assume that VII is formed as a result of methylation of isatin VIII. In fact, an attempt to methylate VIII with dimethyl sulfate in acetic acid did not give positive results. However, when we refluxed III in acetic acid, we were unable to detect even traces of VII, and salt III remained unchanged.



In this case the methylation and contraction processes are probably not simply successive steps but rather are interrelated by a more deep-seated dependence that has not yet been ascertained.

More definite ideas can be expressed relative to the conversion of quinoline I to indoles in alkaline media. One should note the unusual ease of methylation of this compound at the heterocyclic nitrogen atom in aqueous alkali despite the effect of the nitro group. The reason for this is probably the fact that I, being a typical o-nitrophenol, exists in alkaline media in the form of the anion of a nitronic acid [3] in which the negative charge is concentrated on the nitro group [4]. In this case one should expect the participation of the heterocyclic nitrogen atom in delocalization of the negative charge and, as a consequence of this, an increase in its basicity and ease of alkylation. In alkaline media III exists as the following system:



In this limiting structure the electrophilic C_2 atom can undergo intramolecular nucleophilic attack to give a new C_4—C_2 bond. Attack by the hydroxide ion may occur simultaneously. The first pathway leads to indole compound V, while the second leads to pseudobase IV. Similar evidence may also be presented for the ring contraction of I when it is refluxed in alkali without the addition of dimethyl sulfate. The only difference is that a proton from water, which solvates the heteroring with the formation of a hydrogen bond, adds to the heterocyclic nitrogen atom.

It should be noted that the isomerization of 3-hydroxyquinoline to 2-quinolone that we described in [4] is accompanied by the formation of a small amount of indole.

EXPERIMENTAL

The IR spectra of KBr pellets (c = 0.25%) were recorded with UR-20 and UR-10 spectrometers.

Methylation of I in Aqueous Sodium Hydroxide. A 0.76-g (4 mmole) sample of quinoline I was dissolved in 15 ml of a 2 N solution of sodium hydroxide, 2.5 ml of dimethyl sulfate was added, and the mixture was stirred for 8 h and allowed to stand overnight. The following four compounds, which are given in the order of decreasing R_f value, were detected in the reaction mixture by chromatography [on Silufol with dichloroethane–ethyl acetate (4:1)]: traces of V, II, traces of I and IV. The pale-yellow II that precipitated from the alkaline medium was recrystallized from alcohol. The yield of indole II, with mp 154°C (mp 156°C [6]), was 0.41 g (59%). The mother liquor was acidified with concentrated H_2SO_4 to pH 3, and the resulting white precipitate of IV, with mp 200-201°C (from alcohol), was removed by filtration. The yield was 0.07 g (∿8%). Found: C 54.3; H 4.7; N 12.7%. $C_{10}H_{10}N_2O_4$. Calculated: C 54.1; H 4.5; N 12.6%. IR spectrum: 3500-3400, 3230, 1630, 1605, 1530, 1470, 1420, 1405, 1370, 1345, 1295, 1255, 1175, 1130, 1045, 965, 865, 775-755 cm^{-1}. The monobenzoyl derivatives of IV had mp 173.8-174°C (from alcohol). Found: C 62.3; H 4.0; N 8.4%. $C_{17}H_{14}N_2O_5$. Calculated: C 62.1; H 4.3; N 8.6%.

Treatment of III with Aqueous Sodium Carbonate. Solution. A 0.24-g (0.08 mmole) sample of a mixture of sulfates III was stirred in 20 ml of 2 N sodium hydroxide solution at room temperature for 40-50 min, after which 0.09 g (64%) of indole II was removed by filtration. The mother liquor was acidified to pH 3 with concentrated H_2SO_4, and the precipitated IV was separated. The yield was 0.05 g (28%). No melting-point depression was observed for a mixture of N-methyl-3-nitroindole obtained by a known method [5] with a sample of II, and theirIR spectra were identical.

Methylation of Quinoline I in Sodium Carbonate Solution. A mixture of 0.57 g (3 mmole) of quinoline I and 3 ml of dimethyl sulfate in a saturated solution of sodium carbonate was maintained at room temperature for 2 days, and the resulting precipitate was removed by filtration, washed with water, and dried. The yield of V, with mp 191°C (from aqueous alcohol), was 0.24 g (40%). Found: C 58.9; H 4.2; N 13.5%. $C_{10}H_8N_2O_3$. Calculated: C 58.8; H 4.0; N 13.7%. The 2,4-dinitrophenylhydrazone had mp 295-296°C (after repeated washing with hot alcohol). Found: C 50.0; H 3.1; N 21.5%. $C_{16}H_{12}H_6O_6$ [sic]. Calculated: C 50.0; H 3.1; N 21.8%. The filtrate was acidified with sulfuric acid and worked up to give 0.39 g (59%) of IV. In 2 N sodium hydroxide solution V was deformylated to give indole II, which was established by chromatography and a mixed-melting-point determination.

Treatment of III with Aqueous Sodium Carbonate Solution. A 0.24-g (0.08 mmole) sample of a mixture of sulfates III was stirred at room temperature for 40-55 min in 20 ml of a 2 N solution of sodium carbonate, and the precipitate formylindole V was removed by filtration; the yield was 0.08 g (50%). The mother liquor was acidified as in the preceding experiment, and 0.05 g (28%) of IV was isolated. The identical character of II, IV, and V obtained in all of the experiments described above was proved by comparison of the IR spectra and by chromatography.

Methylation of Quinoline I in Glacial Acetic Acid. A 6-ml sample of dimethyl sulfate was added to a solution of 5.7 g of I in 50 ml of acetic acid, and the mixture was refluxed for 1.5-2 h, after which 3 ml of dimethylsulfate was added, and the mixture was refluxed for ∿1 h. It was then cooled, and a light-yellow precipitate containing a mixture of I and III (4.86 g) precipitated. The mixture was dissolved in alcohol, and the solution was passed through a layer of L 100/250μ silica gel with elution with the same solvent to give 1.76 g of starting I. The principal mother liquor was neutralized with a 2 N solution of sodium carbonate, and another 0.69 g of I was removed by filtration. The aqueous filtrate was extracted repeatedly with benzene, after evaporation of which 0.18 g of isatin VII (7.2% based on the converted quinoline I) was isolated. N-Methylisatin was obtained by the method in [6]. No melting-point depression was observed for a mixture of it with a sample of VII, and their IR spectra were identical. Compound III, the anion of which is a mixture of sulfate, bisulfate, and methylsulfate, was removed from the column mechanically with the layer of silica gel and was eluted with several portions of hot alcohol. Evaporation of the solvent gave ∿2 g of a mixture of sulfates III. For analysis, 0.15 g of this mixture was dissolved in hot water, an aqueous solution prepared from 0.16 g of barium oxide hydrate and 0.1 g of p-toluenesulfonic acid was added, and the precipitated barium sulfate was removed by filtration.

The filtrate was evaporated to dryness to give the p-toluenesulfonate with mp 195°C (from water). Found: C 54.4; H 4.3; N 6.9; S 8.7%. $C_{10}H_9N_2O_3 \cdot C_7H_7O_3S$. Calculated: C 54.2; H 4.3; N 7.4; S 8.5%. IR spectrum: 3500-3400, 3070, 3050, 2940, 2900, 2800, 2660, 2550, 2390, 2340, 1640-1600, 1540-1530, 1440, 1375, 1330, 1310, 1275, 1240, 1155, 1115, 1000, 910, 840, 820, 775-760 cm^{-1}.

Treatment of I with Boiling Sodium Hydroxide Solution. A 0.13-g (1 mmole) sample of I was refluxed in 2 N sodium hydroxide solution for 8-10 h, and the resulting precipitate was separated, washed with water, dried, and recrystallized from benzene to give 0.06 g (54.5%) of indole VI with mp 210.5-211°C (mp 210-213°C [2]). No melting-point depression was observed for a mixture of this product with 3-nitroindole obtained by alternative synthesis, and their spectra were identical.

Treatment of I with Boiling Glacial Acetic Acid. A 0.3-g (∿1 mmole) sample of quinoline I was refluxed in 50 ml of glacial acetic acid for 3-4 h, after which the mixture was evaporated to dryness, and the residue was extracted with ether (three 30-ml portions). The ether extract was dried and the ether was removed by distillation. The dry residue was separated with a column filled with L 100/160μ silica gel [elution with benzene—acetone (3:1)]. Isatin VIII was isolated from the first zone, and the yield was 0.08 g (33%); the product had mp 202-203°C (from alcohol) (mp 201-202°C [7]). No melting-point depression was observed for a mixture of this product with a known sample of isatin, and their IR spectra were identical.

LITERATURE CITED

1. K. M. Dyumaev and E. P. Popova, Zh. Org. Khim., 10, 2464 (1974).
2. G. Berti, A. Settimo, and E. Nannipieri, J. Chem. Soc., C, No. 17, 2145 (1968).
3. H. Feuer (ed.), Chemistry of the Nitro and Nitroso Groups, Wiley.
4. K. M. Dyumaev and E. P. Popova, Khim. Geterotsikl. Soedin., No. 6, 859 (1973).
5. L. G. Yudin, A. I. Pavlyuchenko, V. A. Budylin, V. I. Minkin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 11, 1506 (1971).
6. P. Fridlander and S. Kielbansinski, Ber., 44, 3103 (1911).
7. I. P. Wibaut and M. G. Geerling, Rec. Trav. Chim., 50, 41 (1931).

OXIDATION AND HYDROGENATION OF BENZO[g]ISOQUINOLINES

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The oxidation of methyl-substituted (in the pyridine and benzene rings) benzo[g]-isoquinolines to substituted 2-azaanthraquinones was realized. It was established that the pyridine ring is partially reduced to give 1,2,3,4-tetrahydrobenzo[g]isoquinolines in the hydrogenation of benzo[g]isoquinolines in the presence of rhenium heptasulfide.

Natural azaanthraquinones have high biological activity [1]. The patenting of several partially hydrogenated benzo[g]isoquinolines as physiologically active substances has been reported [2]. However, there have been virtually no synthetic studies involving these heterocyclic compounds. Thus, for example, only a few papers [2-4] have been devoted to the preparation of 1,2,3,4-tetrahydrobenzo[g]isoquinolines. The reason for this is that there are as yet no practicable methods for the synthesis of such condensed heterocycles. A method developed for the preparation of benzo[g]isoquinolines by catalytic dehydrocyclization of aryl-γ-pyridylmethanes [5] evidently makes it possible to somewhat expand the study of these compounds.

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